Dual Function of Wnt Signaling during Neuronal Differentiation of Mouse Embryonic Stem Cells.

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Public Summary:
Wn/beta-catenin signaling plays an important role in mouse embryonic stem (ES) cells and neural stem cells. However, it remains unclear how endogenous Wnt/beta-catenin signaling regulates the differentiation of ES cells to neuronal cells. To understand this, we examined the expression profiles of Wnt signaling components. Expression levels of Wnts known to activate beta-catenin signaling were very low in undifferentiated ES cells, whereas they increased during neuronal differentiation of ES cells. Interestingly, activation of Wnt/beta-catenin signaling at different time periods had differential effects on neuronal differentiation of ES cells. Overall, our data suggest that Wnt/beta-catenin signaling plays differential roles at different time points of neuronal differentiation.

Scientific Abstract:
Activation of Wnt signaling enhances self-renewal of mouse embryonic and neural stem/progenitor cells. In contrast, undifferentiated ES cells show a very low level of endogenous Wnt signaling, and ectopic activation of Wnt signaling has been shown to block neuronal differentiation. Therefore, it remains unclear whether or not endogenous Wnt/beta-catenin signaling is necessary for self-renewal or neuronal differentiation of ES cells. To investigate this, we examined the expression profiles of Wnt signaling components. Expression levels of Wnts known to induce beta-catenin were very low in undifferentiated ES cells. Stable ES cell lines which can monitor endogenous activity of Wnt/beta-catenin signaling suggest that Wnt signaling was very low in undifferentiated ES cells, whereas it increased during embryonic body formation or neuronal differentiation. Interestingly, application of small molecules which can positively (BIO, GSK3beta inhibitor) or negatively (IWR-1-endo, Axin stabilizer) control Wnt/beta-catenin signaling suggests that activation of that signaling at different time periods had differential effects on neuronal differentiation of 46C ES cells. Further, ChIP analysis suggested that beta-catenin/TCF1 complex directly regulated the expression of Sox1 during neuronal differentiation. Overall, our data suggest that Wnt/beta-catenin signaling plays differential roles at different time points of neuronal differentiation.